Port J Nephrol Hypert 2015; 29(3): 213-220
Advance Access publication 4 September 2015

Improving erythropoiesis stimulating agents' responsiveness in haemodialysis with less iron: an observational study

Melhorar a resposta aos estimuladores da eritropoiese em hemodiálise com menos ferro: estudo observacional

Patricia Carrilho[1], Marta Alves[2], Ana Martins[1], Ilídio Rodrigues[1]

[1] Nephrocare Barreiro, Clinical Dialysis Unit
[2] Centro Hospitalar Lisboa Central, Epidemiology and Statistics Research Department

Received for publication: 27/02/2015
Accepted in revised form: 30/07/2015

ABSTRACT

Background: Prevalent haemodialysis (HD) patients have functional iron deficiency. Iron supplementation increases erythropoietic stimulating agents (ESA) responsiveness, but concern exists about overload. ESA responsiveness index (ERI) is currently used to quantify resistance to these agents. Frequent administration of a small dose of intravenous (i.v.) iron might improve erythropoiesis, but evidence is lacking. **Methods:** The impact of switching from a variable, intermittent dose of iron sucrose to a frequent (thrice-weekly) fixed dose of 10mg of iron sucrose was assessed in a sequential observational study comparing two periods of 4 months before and 6 months after, in 51 stable haemodialysis patients receiving maintenance iron and ESA (i.v. darbepoetin alfa). **Results:** *Demographics*: mean age 66.2 ± 14 years, dialysis vintage 55 ± 58 months, 21% Black, 43% male. Mean Hb levels (g/dL) during the baseline period (10.9 ± 0.7) did not differ from the study period (11.05 ± 0.6), $p = 0.061$. Iron sucrose dose per patient/month was 203mg (IQR 117-217) during baseline and 130mg during the study period ($p < 0.001$), and the median dose of ESA per patient per month decreased 22% from 90 µg to 70 µg ($p < 0.001$), improving ERI from 6.17 to 4.47 ($p < 0.001$). While ferritin levels did not differ, mean TSAT at the end was significantly higher than at baseline (29.38 ± 10.8 vs. 23.76 ± 8.48 %, respectively, $p < 0.001$), suggesting improved availability of iron for erythropoiesis. Mean total monthly cost (including both i.v. iron and ESA) decreased 25%. **Conclusion:** Administration of less but more frequent iron allowed achieving target Hb, improving ESA response and reducing global costs.

Key Words: Anaemia; darbepoetin alfa; haemodialysis; iron.

RESUMO

Introdução: A suplementação de ferro a doentes em hemodiálise (HD) com défice funcional de ferro aumenta a resposta aos estimuladores da eritropoiese (EE), mas existem preocupações com a possibilidade de sobrecarga. O índice de resposta aos estimuladores de eritropoiese (ERI) permite quantificar a resistência aos EE. A administração frequente de uma pequena dose de ferro endovenoso pode melhorar a eritropoiese, mas não existe evidência para a recomendação desta estratégia. **Métodos:** Avaliou-se o impacto no ERI da mudança de uma dose variável, intermitente, de óxido ferroso sacarosado endovenoso, para uma dose fixa, frequente (3 vezes por semana) de 10mg. Realizou-se um estudo observacional, comparativo de 2 períodos de 4 meses antes (período 1) e 6 meses depois (período 2), em 51 doentes estáveis, em HD sob terapêutica de manutenção com ferro endovenoso (óxido ferroso sacarosado) e EE (darbepoetina alfa endovenosa). **Resultados:** idade 66,2 ± 14 anos, *vintage* de diálise 55 ± 58 meses, 21% melanodérmicos, 43% sexo masculino. A média da hemoglobina Hb (g/dL) no período 1 (10,9 ± 0,7) não diferiu do período 2 (11,05 ± 0,6), $p = 0{,}061$. A dose de ferro por doente/mês foi 203mg (IQR 117--217) durante o período 1 e 130mg no período 2 ($p < 0{,}001$). A dose mensal de EE diminuiu de 90 µg para 70 µg ($p < 0{,}001$), melhorando o ERI de 6,17 para 4,47 ($p < 0{,}001$). Enquanto os níveis de ferritina não diferiram, a média da TSAT no final foi superior à inicial (29,38 ± 10,8 *vs.* 23,76 ± 8,48), respectivamente, $p < 0{,}001$), sugerindo melhoria da disponibilidade do ferro para a eritropoiese. A média dos custos mensais (incluindo o ferro e o EE) diminuiu 25%. **Conclusão:** A administração de menos ferro de forma mais frequente permitiu atingir o valor alvo de Hb, melhorando a resposta ao EE e reduzindo os custos globais.

Palavras-Chave: Anemia; darbepoetina alfa; ferro; hemodiálise.

INTRODUCTION

Optimizing anaemia treatment in HD patients remains a priority worldwide, as it has significant health and economic implications. As successful use of ESA requires sufficient available iron before and during therapy, almost all HD patients on ESA receive i.v. iron therapy[1]. Mobilization of iron from storage sites is often inadequate, and many prevalent dialysis patients are classified as having functional iron deficiency, as they benefit from further iron administration even if storage sites are replete[2,3].

It is widely considered that iron overload among dialysis patients was more prevalent during the pre--ESA era, when blood transfusion was frequent and i.v. iron therapy was given without concomitant ESA administration[4-6]. Parenteral iron supplementation is increasing in HD patients in the US and Europe[7-9], following actual guidelines[10-13] that suggest increasing iron to allow reduction of ESAs to treat anaemia. Retrospective studies have linked higher doses of i.v. iron administration with increased mortality and morbidity[14-18]. Long-term randomized clinical trials are required to explore the effects of i.v. iron on outcomes in HD patients[12,13,17,18]. An increasing number of studies show that today, a significant proportion of patients receiving iron and ESA according to the current guidelines have iron hepatic overload, as assessed by MRI[19-21].

Erythropoiesis is a continuous process where iron is incorporated in erythrocyte precursors when bound to transferrin[22,23]. Frequency of iron administration seems to be an important factor for anaemia treatment optimization[24-29], as availability of iron for erythropoiesis might increase. Response to iron therapy can be measured by ESA responsiveness index (ERI), calculated as ESA dose (IU)/weight (kg)/ week divided by a given value of haemoglobin (Hb) concentration (g/dl)[30].

Hepcidin is elevated in chronic kidney disease and blocks both the absorption of oral iron and the release of stored iron from reticuloendothelial macrophages by degrading the iron exporter ferroportin[1,22].

On the other hand, one of hepcidin's production stimulus is iron itself[23], regulated by the expression of two mechanisms: liver iron stores and circulating iron levels. Frequent administration of a small dose of i.v. iron could, thus, improve erythropoiesis[27], although, at present, evidence is lacking to recommend any different strategy of iron administration[12,13,31]. Blood losses during haemodialysis-related procedures can vary from 1 to 5g of elemental iron per year, where patient-dependent factors and centre practices (such as blood circuit final rinsing) are determinant[1]. Attempts to estimate the optimal dose of iron to match stable patients with chronic kidney disease stage 5 on regular HD or haemodiafiltration (HDF) treatment needs are challenging[32,33]. Safety concerns about excessive iron administration[34], have led us to test the hypothesis that a smaller frequently administered amount of iron improves erythropoiesis in prevalent patients.

Our practice changed to providing frequent (thrice--weekly) maintenance dose of 10mg i.v. iron sucrose to stable patients where major blood losses are not evident, disregard of ferritin levels if they are between 150 and 500 ng/mL. Those with ferritin levels between 500 and 600ng/dL were included if TSAT was ‹ 30%. This article is meant to share our results with this practice.

SUBJECTS AND METHODS

This was an observational, single-centre, single--cohort study. The study was held in 2012 and comprised two time periods: 4 months before (baseline period) and 6 months after switch to more frequent iron schedule, at the fixed i.v. dose of 10mg of iron sucrose thrice-weekly (study period). Anaemia treatment with iron sucrose during baseline period was determined by each nephrologist analysis of patients' laboratory determinations of haemoglobin (Hb) levels and tendencies, taking into account ferritin and transferrin saturation (TSAT) determinations, as suggested by international guidelines[28-30].

Medical management did not otherwise change during the study period, and ESA prescription was adjusted monthly according to the target Hb of 10-13g/dL, as usual practice. Data during the baseline period were obtained retrospectively from the patients' medical records, and subsequent data were collected prospectively.

Objectives

The primary objective was to compare the impact on ESA responsiveness of the switch from a variable, intermittent dose of iron sucrose given on an less frequent schedule (time intervals equal to or higher than once weekly) to a more frequent (thrice-weekly) fixed dose of 10mg of iron sucrose to treat anaemia in a population with chronic kidney disease stage 5 on HD/HDF treatment.

The secondary objectives were to describe the level of i.v. iron and ESA drugs consumption and to estimate anaemia drug expenditure for the two treatment periods.

Patients

Adult patients undergoing HD/HDF for more than 6 months at the centre were included in the analysis, if they were under ESA (darbepoetin), had Hb levels between 9 and 13g/dL and ferritin between 150 and 600 ng/mL. Those with ferritin › 500 and ‹ 600ng/dL were included only if TSAT was ‹ 30%.

Exclusion criteria were: participation in other studies, known haematological disease, active oncological disease, recent surgery or blood transfusion (last 16 weeks).

ESA (darbepoetin) was injected i.v. once weekly. Iron sucrose used was Venofer®.

Evaluation

The Hb was assessed every month. Transferrin saturation (TSAT) and serum ferritin were measured at the beginning and the end of the study (6 months interval).

Statistical analysis

Data were expressed as numbers (or percentages) for categorical variables, mean ± SD for continuous

normally distributed variables, median and inter-quartile range (IQR) for continuous non-normally distributed variables. Between-period comparisons were performed using paired students' *t*-test for normal variables and the paired Wilcoxon test for continuous data with non-normal distribution. A *p*-value ‹ 0.05 was considered as statistically significant.

The data were entered into a database and analysed with v. 13.0 of the SPSS (SPSS Inc., Chicago, Illinois, USA).

Table I

Baseline demographic and clinical characteristics

Age (years)	66,2 ± 13,8 (33-95)
Gender (mal/female)	22 / 29 (43%)
Ethnicity (black/white)	11 / 40 (21% black)
Dialysis vintage (months)	55,06 ± 58,4
PTHi (pg/mL)	472,7 ± 336,05
Charlson Index	6,58 ± 2,33
Primary Renal Disease	27% Diabetes / 23% Hypertension / 21% Glomerulonephritis / 29% other

RESULTS

Patient population

Of 219 patients receiving dialysis at the centre, 57 were eligible for inclusion in the analysis and started a fixed dose of 10mg of i.v. iron sucrose thrice weekly, during dialysis. There were 53 other patients who were otherwise eligible but participating in another study. Six patients were excluded from the final analysis because of death (one), transplant (one), oncological disease requiring radiotherapy (three) or prolonged absence to dialysis, defined as › 10 days (one), leaving 51 patients. Forty-nine patients were on regular HDF treatment and the remaining were on HD. The demographics and clinical profile of the population are described in Table I.

During baseline, iron sucrose administration was extremely variable, as it depended on each nephrologist's criteria, according to Hb tendencies and laboratory iron parameters.

Efficacy

Haemoglobin

Mean Hb levels (g/dL) during baseline period (10.9 ± 0.70) did not differ from the study period (11.05 ± 0.59), shown in Fig. 1, (p = 0.061).

ESA consumption and responsiveness index (ERI)

The monthly dose of darbepoetin per patient lowered from 90 µg(IQR 65 – 142.5) during baseline to

Figure 1

Mean Hb levels did not differ, as expected, since ESA's prescription was targeting Hb between 10-13g/dL in both study periods.

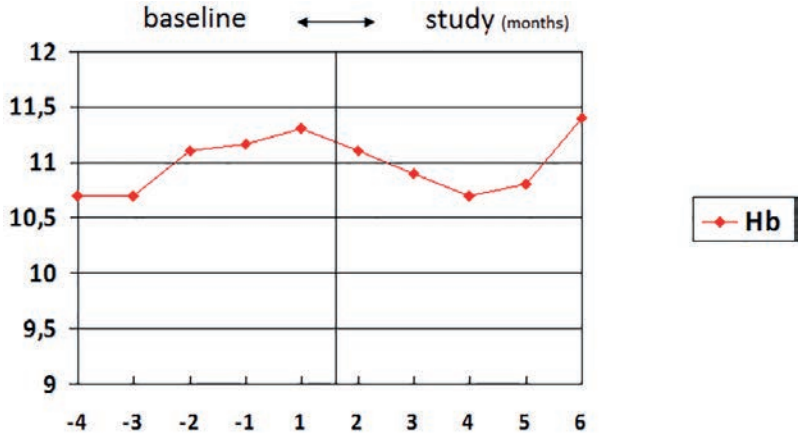
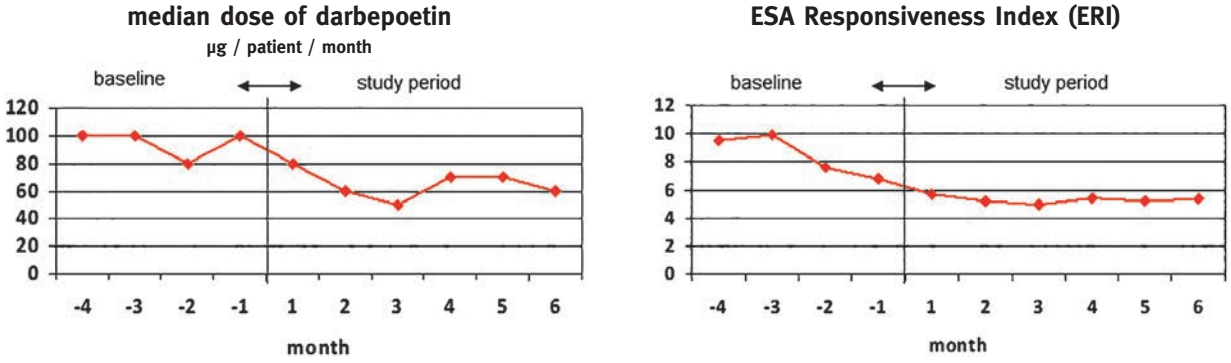


Figure 2

ESA's dose lowered 22% and ERI improved significantly during frequent low dose iron administration.



70 µg (IQR 46.7 – 90) during the period study (p < 0.001), representing a 22% decrease (Fig. 2]).

According to body weight, the monthly dose of darbepoetin was 1,37 (IQR 0,96 – 1.37) and 1.146 µg (IQR 0.71- 1,47) g respectively, during baseline and period study (p < 0.001), representing a 17% decrease. As expected, ERI during the period study was significantly lower (4.468, IQR 3.01-6.03) than baseline (6.169 IQR 4.29-9.88, p < 0.001) (Fig. 2).

Iron parameters

Intravenous iron consumption

The median iron sucrose dose per patient/month was 203.3 mg (IQR 116.7-216.7) during baseline, while during the study period, the iron dose was fixed, totalizing 130mg/month (p < 0.001) (Fig. 3). This represented a decrease of 36%, which was also significantly different when calculated taking patient weight into account: 2.86 mg/Kg/month (IQR 1.95--3.71) vs. 1.96 (IQR 1.68-2.18, p < 0.001).

Ferritin and transferrin saturation

Mean TSAT at the end was significantly higher than at baseline (29.38 ± 10.8 vs. 23.76 ± 8.48 %, respectively, p < 0.001) (Table II).

Mean ferritin levels did not differ during both treatment periods (389.3 ± 120.6 at baseline and 385.3 ± 192.2 ng/mL at the end of the study period, p = 0.876).

Figure 3

The median iron sucrose dose per patient/month decreased from 203.3 to 130mg (p < 0.001).

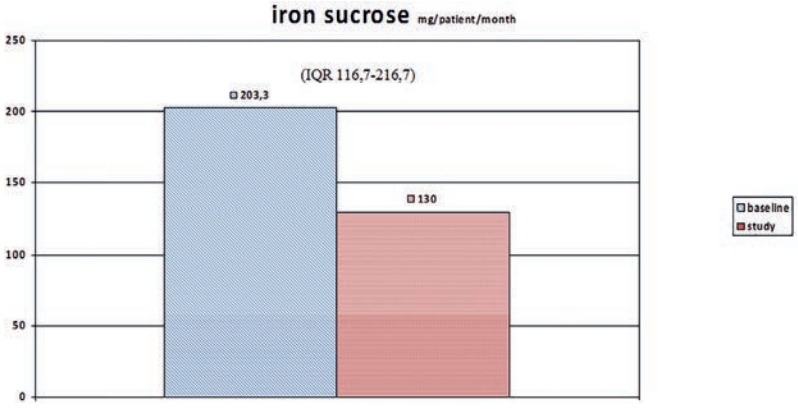


Table II

Ferritin and TSAT at the beginning and at the end of the study

Mean ± SD	Baseline Period	Study Period	P-value
Serum ferritin (ng/dL)	389,3 ± 120,6	385,3 ± 192,2	P = 0,876
TSAT %	23,76 ± 8,48	26,38 ± 10,8	P < 0,001

Economic impact

The cost of i.v. iron and ESA medications over time was calculated for both periods. The unit cost of i.v. iron (public price) at the time was 12.26 €/ampoule (100 mg iron sucrose Venofer®) and the cost of darbepoetin (public price) was 1.344 €/µg. Results were extrapolated to obtain a yearly saving cost per patient by multiplying the mean monthly cost per patient by 12. This extrapolation is only indicative as unit cost estimates are centre specific, especially concerning darbepoetin.

The cumulative cost of i.v. iron was 24.9 €/month/patient during baseline and 15.,9 € during the study period. For ESA, the mean monthly cost per patient was 121€ during baseline and 94 € during the study period. The total cost per patient from the health care provider's perspective (including both i.v. iron and ESA) was 146 € and 110 € during baseline and the study period, respectively (25% decrease – Fig. 4). The cost savings of switching from intermittent administration of 100mg of iron sucrose to frequent/thrice weekly 10mg of iron sucrose for 1 year was estimated to be about 432€ per patient.

DISCUSSION

The ESA resistance (ERI) is a strong, independent mortality risk factor in haemodialysis[35-37]. In this population of stable HD patients, after switching to a fixed, frequent administration of low dose i.v. iron sucrose, Hb target was achieved, with a 22% reduction of absolute ESA dose/month.

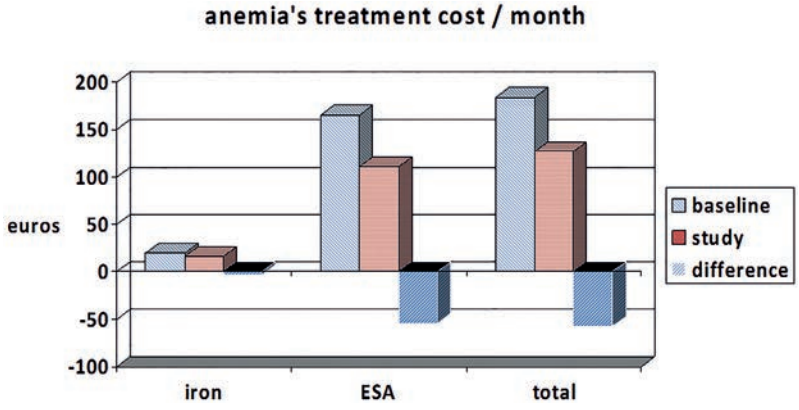
A previous observational study[30] has shown a relationship between ERI and Charlson comorbidity index. In this study's population, the mean Charlson comorbidity index was 6.58 ± 2.33. Baseline ERI was already low (6.169), considering comorbidities, and it improved to 4.468.

In the present study, the median monthly dose of iron supplied during the study period was lower than the dose given during the baseline period to these patients, so these results were achieved using less iron. Mean ferritin levels were similar, but transferrin saturation improved, probably meaning a more efficient transport of available iron to the bone marrow. Although other studies have suggested benefit in providing frequent low dose maintenance i.v. iron to HD patients[24-29], this is, to our knowledge, the study with the greatest number of patients.

An improved erythropoietic response was achieved after switching to the dose of 10mg of iron sucrose thrice weekly. Other studies have found similar iron needs. Soluble ferric pyrophosphate delivers iron via dialysate slowly during dialysis treatment and

Figure 4

The total monthly cost of anaemia treatment (iron and ESA) per patient was 146 € and 110 € during baseline and the study period, respectively, a difference of 36 € (25% decrease).



replaces 5-7 mg of iron lost during each treatment to maintain iron balance[38,39]. The KDOQI guidelines and recommendations propose consistent IV iron administration at 22–65 mg per week[11]. Sources of ongoing iron loss include blood retention in the dialyser and tubing, that can and should be minimized by good rinsing practices, whose importance should be emphasized. The i.v. iron infusion with various formulations in humans results in an early increase in transferrin saturation, total serum iron, and NTBI levels followed by an increase in ferritin levels several days later[40-43]. However, some iron can bypass the RES and directly bind to transferrin[41]. *In vitro* studies estimate that up to 6% of i.v. iron bypasses RES processing[43]. Maybe the increased efficacy of frequent administration strategy is partly due to this mechanism. Another possible and speculative explanation for the increased efficacy could be that the so-called "low-dose" might circumvent hepcidin's increase in response to iron i.v. administration, contributing to enhanced utilization of given iron. Lower doses of iron therapy are welcome, as iron overload is known to promote endothelial dysfunction, cardiovascular disease, and immune dysfunction which are the leading causes of premature mortality in HD patients. Many studies have shown a strong association of ESA resistance with inflammation, not accomplished in this analysis, as it was not the focus of the present study, and for which a larger sample of patients would have to be considered.

This was an observational study, where baseline period was studied retrospectively. Iron administration was made according to each nephrologist's usual practice during that period. As such, these results may not be reproducible in other clinical contexts. This study can be criticized as it did not include determination of transferrin saturation and ferritin levels every 3 months, as suggested by current guidelines. Its main purpose was to evaluate an alternative strategy of iron administration, where determination of iron parameters and eventual changing of prescription at 3 months would be premature. Current guidelines, although prudent recommending frequent evaluation of iron parameters, have led to a worrying increase in iron administration worldwide[9], with notable increases in ferritin but not TSAT levels. With the rising cumulative i.v. iron doses, studies of the effects of changing i.v. iron dosing and other anaemia management practices on clinical outcomes should be a high priority[9,12,13], and the search of alternative strategies should be an urgent quest. These results suggest that supplying a constant, frequent, maintenance low dose of i.v. iron may be more adequate for the patient (since it may spare ESA's and iron's higher doses and their secondary effects). Concerns whether continuous iron supplementation leads to positive iron balance instead of a steady state[29], can be argued against, as ESA's responsiveness increased with less iron being supplied, suggesting that iron was used in erythropoiesis, not stored in deposits. Nowadays this question can be assessed by MRI[21] to evaluate hepatic iron deposits in these patients, although it is still prohibitively expensive for use in the clinical practice. The economic impact of this strategy was welcome, as anaemia drug expenditure decreased by 25% in these patients.

In conclusion, in this study, although less iron was administered, the target Hb was achieved and ESA's response improved, suggesting that administration of low frequent doses of i.v. iron might improve iron's utilization in erythropoiesis. Prospective comparative clinical trials should test this hypothesis, as it may spare dialysis patients the administration of unnecessary iron, overloading stores that are not being efficiently used in erythropoiesis.

ACKNOWLEDGEMENTS

The authors gratefully acknowledge the contributions of the nursing staff from Nephrocare Barreiro, Clinical Dialysis Unit.

Conflict of interest statement: None declared.

References

1. Hörl WH. Clinical aspects of iron use in the anemia of kidney disease. J Am Soc Nephrol 2007; 18(2): 382-393.

2. Coyne DW, Kapoian T, Suki W, *et al.* with the DRIVE Study Group. Ferric gluconate is highly efficacious in anemic hemodialysis patients with high serum ferritin and low transferrin saturation: results of the Dialysis Patients' Response to IV Iron with Elevated Ferritin (DRIVE) Study. J Am Soc Nephrol 2007; 18(3):975-984.

3. Kshirsagar AV, Freburger JK, Ellis AR, Wang L, Winkelmayer WC, Brookhart MA. The comparative short-term effectiveness of iron dosing and formulations in US hemodialysis patients. Am J Med 2013; 126(6): 541.e1–541.e14.

4. Ali M, Fayemi AO, Rigolosi R, Frascino J, Marsden T, Malcolm D. Hemosiderosis in hemodialysis patients. An autopsy study of 50 cases. JAMA 1980;244(4):343-345.

5. Pitts TO, Barbour GL. Hemosiderosis secondary to chronic parenteral iron therapy in maintenance hemodialysis patients. Nephron 1978; 22(4-6): 316-321.

6. Gokal R, Millard PR, Weatherall DJ, Callender ST, Ledingham JG, Oliver DO. Iron metabolism in hemodialysis patients. A study of the management of iron therapy and overload. Q J Med 1979; 48(191): 369-391.

7. Miskulin DC, Zhou J, Tangri N, *et al.* with the DEcIDE Network Patient Outcomes in End-Stage Renal Disease Study Investigators. Trends in anemia management in US hemodialysis patients 2004–2010. BMC Nephrol 2013; 14: 264.

8. Freburger JK, Ng LJ, Bradbury BD, Kshirsagar AV, Brookhart MA. Changing patterns of anemia management in US hemodialysis patients. Am J Med 2012; 125(9): 906–914.

9. Bailie GR, Larkina M, Goodkin DA, *et al.* Variation in intravenous iron use internationally and over time: the Dialysis Outcomes and Practice Patterns Study (DOPPS). Nephrol Dial Transplant 2013; 28(10): 2570-2579.

10. IV. NKF-K/DOQI Clinical Practice Guidelines for Anemia of Chronic Kidney Disease: update 2000. Am J Kidney Dis 2001; 37(1 Suppl 1): S182-S238.

11. K/DOQI Clinical practice guidelines and clinical practice recommendations for anemia in chronic kidney disease. Am J Kidney Dis 2006; 47 (5 Suppl 3): S11-145.

12. Kidney Disease: Improving Global Outcomes (KDIGO) Anemia Work Group. KDIGO clinical practice guideline for anemia in chronic kidney disease. Kidney Int Suppl. 2012;2(4):279-335.

13. Locatelli F, Bárány P, Covic A, *et al.* Kidney Disease: Improving Global Outcomes guidelines on anaemia management in chronic kidney disease: a European Renal Best Practice position statement. Nephrol Dial Transplant 2013; 28(6): 1346-1359.

14. Brookhart MA, Freburger JK, Ellis AR, Wang L, Winkelmayer WC, Kshirsagar AV. Infection risk with bolus versus maintenance iron supplementation in hemodialysis patients. J Am Soc Nephrol 2013; 24(7):1151-1158.

15. Feldman HI, Joffe M, Robinson B, *et al.* Administration of parenteral iron and mortality among hemodialysis patients. J Am Soc Nephrol 2004; 15(6):1623-1632.

16. Kalantar-Zadeh K, Regidor DL, McAllister CJ, Michael B, Warnock DG. Time-dependent associations between iron and mortality in hemodialysis patients. J Am Soc Nephrol 2005; 16(10):3070-3080.

17. Van Buren P, Velez RL, Vaziri ND, Zhou XJ. Iron overdose: a contributor to adverse outcomes in randomized trials of anemia correction in CKD. Int Urol Nephrol 2012;44(2):499-507.

18. Susantitaphong P, Alqahtani F, Jaber BL. Efficacy and safety of intravenous iron therapy for functional iron deficiency anemia in hemodialysis patients: a meta-analysis. Am J Nephrol 2014; 39(2):130-141.

19. Ferrari P, Kulkarni H, Dheda S, *et al.* Serum iron markers are inadequate for guiding iron repletion in chronic kidney disease. Clin J Am Soc Nephrol 2011; 6(1):77-83.

20. Canavese C, Bergamo D, Ciccone G, *et al.* Validation of serum ferritin values by magnetic susceptometry in predicting iron overload in dialysis patients. Kidney Int 2004; 65(3):1091-1098.

21. Rostoer G, Griuncelli M, Loridon C, *et al.* Hemodialysis-associated hemosiderosis in the era of erythropoiesis-stimulating agents: a MRI study. Am J Med 2012; 125(10): 991-999.

22. Weiss G, Goodnough LT. Anemia of chronic disease. N Engl J Med 2005;352(10):1011-1023.

23. Fleming RE, Ponka P. Iron overload in human disease. N Engl J Med 2012; 366(4):348--359.

24. Silva J, Andrade S, Ventura H, *et al.* Iron supplementation in haemodialysis– practical clinical guidelines. Nephrol Dial Transplant 1998; 13(10): 2572-2577.

25. Saltissi D, Sauvage D, Westhuyzen J. Comparative response to single or divided doses of parenteral iron for functional iron deficiency in hemodialysis patients receiving erythropoetin (EPO). Clin Nephrol 1998; 49(1):45-48.

26. Agarwal R, Davis JL, Hamburger RJ. A trial of two iron dextran infusion regimens in chronic hemodialysis patients. Clin Nephrol 2000; 54(2): 105-111.

27. Bolaños L, Castro P, Falcon TG, Mouzo R, Varela JM. Continuous intravenous sodium ferric gluconate improves efficacy in the maintenance phase of EPO rHu administration in hemodialysis patients. Am J Nephrol 2002; 22(1): 67-72.

28. Giordano A, Arrigo G, Lavarda F, Colasanti G, Petrini C. Comparison of two iron gluconate treatment modalities in chronic hemodialysis patients: results of a randomized trial. J Nephrol 2005; 18(2): 1-7.

29. Canavese C, Bergamo D, Ciccone G, *et al.* Low-dose continuous iron therapy leads to a positive iron balance and decreased serum transferrin levels in chronic haemodialysis patients. Nephrol Dial Transplant 2004; 19(6): 1564–1570.

30. Lopez-Gomez JM, Portolés JM, Aljama P. Factors that condition the response to erythropoietin in patients on hemodialysis and their relation to mortality. Kidney Int Suppl 2008;74 (111): S75-S81.

31. Singh A. Hemoglobin control, ESA resistance, and regular low-dose IV iron therapy: a review of the evidence. Semin Dial 2009; 22(1): 64-69.

32. Sargent JA, Acchiar SR. Iron requirements in hemodialysis. Blood Purif 2004; 22(1): 112-123.

33. Eschbach JW, Cook JD, Scribner BH, Finch CA. Iron balance in hemodialysis patients. Ann Intern Med 1977; 87(6): 710-713.

34. Yamamoto H, Tsubakihara Y. Limiting iron supplementation for anemia in dialysis patients – the Basis for Japan's conservative guidelines. Semin Dial 2011; 24(3): 269--271.

35. Kilpatrick RD, Critchlow CW, Fishbane S, et al. Greater epoetin alfa responsiveness is associated with improved survival in hemodialysis patients. Clin J Am Soc Nephrol 2008;3(4):1077-1083.

36. Zhang Y, Thamer M, Stefanik K, Kaufman J, Cotter DJ. Epoetin requirements predict mortality in hemodialysis patients. Am J Kidney Dis 2004; 44(5):866-876.

37. Kainz A, Mayer B, Kramar R, Oberbauer R. Association of ESA hypo-responsiveness and haemoglobin variability with mortality in haemodialysis patients. Nephrol Dial Transplant 2010; 25(11):3701-3706.

38. Gupta A, Amin NB, Besarab A, *et al.* Dialysate iron therapy: infusion of soluble ferric pyrophosphate via the dialysate during hemodialysis. Kidney Int 1999;55(5):1891-1898.

39. Guss CD, Farmer TM, Gupta A, *et al.* Soluble ferric pyrophosphate (SFP) administered via dialysate showed no acute safety signals. [Abstract] J Am Soc Nephrol 2013;24:218A.

40. Zanen AL, Adriaansen HJ, Bommel EF, Posthuma R, Th de Jong GM. 'Oversaturation' of transferrin after intravenous ferric gluconate [Ferrlecit(R)] in haemodialysis patients. Nephrol Dial Transplant 1996; 11(5):820–824.

41. Kooistra MP, Kersting S, Gosriwatana I, *et al.* Nontransferrin-bound iron in the plasma of haemodialysis patients after intravenous iron saccharate infusion. Eur J Clin Invest 2002; 32(Suppl 1):36–41.

42. Henderson PA, Hillman RS. Characteristics of iron dextran utilization in man. Blood 1969; 34(3):357–375.

43. Van Wyck D, Anderson J, Johnson K. Labile iron in parenteral iron formulations: a quantitative and comparative study. Nephrol Dial Transplant 2004; 19(3):561–565.

Correspondence to:
Drª Patrícia S. Carrilho
NephroCare Barreiro
Rua José Saramago 4Planalto dos Casquilhos
2830-555 Barreiro, Portugal.
E-mail: patricia.s.carrilho@hff.min-saude.pt